Effects of Temperature on Convulsive Liability of Pentylenetetrazol, Strychnine Sulfate, and Thebaine Hydrochloride

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The CD_{50}'s of pentylenetetrazol, strychnine, and thebaine were determined by intraperitoneal injection into white mice after 1-hr. exposure to ambient temperatures of 6, 16, 22, 24, 30, and 35°. Rectal temperatures were also measured. The data are interpreted on the basis of the pharmacology of the compounds used and the observed effects of temperature on the actions of these compounds.

THE INFLUENCE of body temperature and environmental temperature on the potency of central nervous system (CNS) stimulants has been studied by several investigators (1–5). The amount of information available on the effect of temperature on drug action is considerable; however, due to the variations in experimental design the correlation between the work of different researchers is not so clear cut as would be desirable. Indeed, there are more than a few cases of apparent contradiction. To cite but a few: Chen *et al.* (1) reported that the convulsive dose 50 (CD_{50}) of strychnine sulfate in mice was unaltered by changes in environmental temperature from 20 to 40°. Bogdanovic (2) found the toxicity of strychnine to be decreased in rats which had been cooled to 16–18° by the Giaja method. Bogdanovic also reported that the toxicity of pentylenetetrazol (PTZ) was unaltered by hypothermia. Bogdanovic suggests that the different responses to drugs produced by hypothermia may be related to the different levels of the CNS at which the drugs act. This would explain in part his observation that pentylenetetrazol, which acts at numerous levels of the neural axis, is unaltered by a decrease in body temperature.

However, Swinyard and Toman (3) found the susceptibility to convulsions induced by pentylenetetrazol to be increased by lowering the body temperature (*cf. References 4, 5*). This does not necessarily mean that Bogdanovic is wrong in his contention that the temperature-potency relationship is influenced by the level(s) of the CNS at which drugs act. Should his contention be true, it would be expected that two agents which act in a similar manner such as strychnine and thebaine (7) would produce similar responses upon a change in environmental temperature. Furthermore, both compounds should differ from pentylenetetrazol. This study tests such an hypothesis.

Fuhrman and Fuhrman (6) in their excellent review on the effects of temperature on the action of drugs attribute the importance of environmental temperature mainly to the changes it invokes in body temperature. Assuming this to be true, it should be possible to determine the minimum change in body temperature which will result in a significant variation in response to a given drug. If this minimum change were consistent over a wide range of body temperatures, a predictability would exist that would simplify considerably the interpretation of any data which might be gathered over a wide environmental temperature range. This study was undertaken to see if such a predictability exists.

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EXPERIMENTAL

Pentylenetetrazol, thebaine hydrochloride, and strychnine sulfate were dissolved separately in distilled water and injected intraperitoneally into male mice of the Swiss albino strain weighing between 14 and 37 Gm. The mice were exposed to environmental temperatures of 6, 16, 22, 24, 30, and 35° for 1 hr. prior to injection of the compounds. Fifty mice/compound/temperature were used to determine the convulsive dose 50 (CD_{50}). Ten additional mice/environmental temperature were employed in determining the mean rectal temperature. All data were evaluated by the statistical method of Litchfield and Wilcoxon (8).

RESULTS AND DISCUSSION

This experiment was designed to study the relationship between temperature (environmental and rectal) and convulsive liability of PTZ, strychnine sulfate, and thebaine hydrochloride. The relatively short time of exposure (1 hr.) was used to minimize the adaptation of the animals to the stresses of the environmental temperatures employed in this study. The results are shown in Table I. Across temperature comparisons are presented in Table II.

Pentylenetetrazol.—Table I shows that the CD_{50} of PTZ rose progressively with the temperature. As can be seen in Table II, the CD_{50} of PTZ was not significantly different at environmental temperatures of 16 through 30°. All other combinations of environmental temperatures compared revealed significant differences in the CD_{50}'s.

Table II shows that the minimum change in rectal temperature which was accompanied by a significant alteration of the CD_{50} of PTZ was 1°. However, an increase in ambient temperature from 6 to 16° raised the rectal temperature 1.7° but did not alter significantly the CD_{50}. In all cases where rectal temperatures differed by 1.8° or more there were significant changes in the CD_{50} of PTZ.

The data for the PTZ portion of this experiment are not in accord with those of Bogdanovic (2) and Braun and Lusky (5), but do agree with those of Swinyard and Toman (3).

Strychnine.—The CD_{50} of strychnine sulfate differed significantly only between the extremes of the ambient temperatures studied and was significantly larger at 35° than at 6°. As expected, the greatest change in rectal temperature (4.2°) occurred between these two environmental temperatures (Table II).

In the case of strychnine the results of the present experiment are at variance with the work of Chen *et al.* (1), who found the CD_{50} and LD_{50} of strych-

TABLE I.—EFFECTS OF TEMPERATURE ON THE CD_{50} OF PENTYLENETETRAZOL, STRYCHNINE SULFATE, AND THEBAINE HYDROCHLORIDE

No.	Temp., °C. Environmental	Temp., °C. Rectal	CD_{50}, mg./Kg. Pentylenetetrazol	CD_{50}, mg./Kg. Strychnine	CD_{50}, mg./Kg. Thebaine
1	6	33.5	48.0	0.96	16.8
2	16	35.2	50.0	1.19	17.0
3	22	35.3	52.0	1.28	16.5
4	24	36.5	52.0	1.29	19.0
5	30	36.7	53.0	1.29	20.5
6	35	37.7	62.5	1.58	17.0

TABLE II.—ACROSS TEMPERATURE COMPARISON OF THE EFFECT OF CHANGES IN TEMPERATURE ON THE CD_{50} OF PENTYLENETETRAZOL, STRYCHNINE SULFATE, AND THEBAINE HYDROCHLORIDE

Temp. Range, °C. Environmental	Change in Rectal Temp., °C.	Remarks PTZ	Remarks Strychnine	Remarks Thebaine
6–16	1.7	0[a]	0	0
6–22	1.8	+[b]	0	0
6–24	3.0	+	0	+
6–30	3.2	+	0	+
6–35	4.2	+	+	0
16–22	0.1	0	0	+
16–24	1.3	0	0	+
16–30	1.5	0	0	+
16–35	2.5	+	0	0
22–24	1.2	0	0	+
22–30	1.4	0	0	+
22–35	2.4	+	0	0
24–30	0.2	0	0	+
24–35	1.2	+	0	0
30–35	1.0	+	0	+

[a] 0, Indicates no statistically significant alteration of the CD_{50}. [b] +, Indicates a statistically significant alteration of the CD_{50}.

nine to be unaltered by changes in temperature from 20 to 40°. This disagreement may be due in part to the use of a smaller temperature range on the part of Chen *et al.*

Thebaine.—The CD_{50} of thebaine hydrochloride was significantly larger at 30° than at all other environmental temperatures studied. Any change in ambient temperature from this point resulted in a decrease in the CD_{50} of the compound. A change in rectal temperature of 1.7° which occurred between environmental temperatures of 6° and 16° was not accompanied by a significant change in the CD_{50}. On the other hand, a significant difference in the CD_{50} did exist between ambient temperatures of 16 and 22°, although rectal temperature differed by only 0.1° between these two points (Table II). The maximum change in the CD_{50} was obtained between ambient temperatures of 22 and 30° with the CD_{50} being significantly greater at the latter temperature. No references were found concerning the effect of temperature on the CD_{50} of thebaine.

Strychnine and thebaine did not respond to temperature changes in a qualitatively similar manner, although both are reported to act at the same level of the CNS (7). This does not agree with Bogdanovic, who contends that CNS stimulants respond to changes in temperature in accordance with their levels of activity (2).

SUMMARY AND CONCLUSIONS

A study was conducted in order to determine the effects of environmental and body temperatures on the CD_{50} of pentylenetetrazol (PTZ), strychnine sulfate, and thebaine hydrochloride in mice. No correlation was found between the levels of action of the compounds in the CNS and the influence of temperature on their CD_{50}'s. Furthermore, no predictability was found to exist with regard to the minimum change in body temperature which resulted in a significant change in the CD_{50} of any of the compounds studied. The CD_{50}'s of pentylenetetrazol and strychnine sulfate increased as the temperature rose. Thebaine on the other hand had a maximum CD_{50} at an environmental temperature of 30°. The CD_{50} dropped sharply at temperatures both above and below this point.

In conclusion, changes in body temperature produced by varying the ambient temperature are of fundamental importance. However, no predictability exists with regard to the minimum change in body temperature which will result in a significant alteration in the CD_{50} of the compounds studied in this experiment. Finally, little can be said from this experiment about the nature of the influence of temperature on the action of these compounds.

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